UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/829,491	04/22/2004	Ing-Ming Chiu	28489/04001	7628

24024 7590 03/10/2005

CALFEE HALTER & GRISWOLD, LLP
800 SUPERIOR AVENUE
SUITE 1400
CLEVELAND, OH 44114

EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/829,491	CHIU, ING-MING	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,15-33 and 37-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,15-33 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/22/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

DETAILED ACTION

Applicant's response to the Restriction was received on 12/20/2004. Claims 1-11, 15-33 and 37-40 are pending in the instant application. Applicant's election with traverse of the invention of group I claims 1-11 and 15-33, drawn to a non-human, transgenic mammal, a cell line derived from said mammal, and an *in vivo* method for using said mammal for identifying a drug which is effective at inhibiting the growth of brain tumors in a mammal, without traverse, in the reply filed on 12/20/2004 is acknowledged. Applicant canceled claims 12-14, 34-36 and added claims 37-40. Applicant should note that the examiner of record is now Louis D. Lieto of ART Unit 1632.

Claims 1-11, 15-33 and 37-40 are currently under examination.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2), see, SEQ ID No. 3. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures which is attached to this communication. Specifically, SEQ ID No. 3 requires submission as a computer readable form copy.

This application clearly fails to comply with requirements of 37 C.F.R 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23,1998). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the *Federal Register* at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000). Applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy or compact disc copy of the "Sequence Listing", as well as an amendment directing its entry into application. Applicant must also provide a statement that the content of the sequence listing information recorded in computer readable format is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 C.F.R. 1.821 (e), 1.821 (f), 1.821 (g), 1.825 (b), 1.825 (d). If applicant desires the sequence listing in the instant application to be identical with that of another application on file in the Patent and Trademark Office, such request in accordance with 37 C.F.R. 1.821(e) may be submitted in lieu of a new CRF.

For the response to this action to be complete, Applicants are required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6, 7, 9, 10, 15-18, 20-22, 25, 26, 28, 29, 31-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3,9,10,15-18, 20-22, 28, 29, 31-33 are drawn to a mammal comprising a transgene comprising an active portion of any FGF1B promoter linked to a sequence encoding the SV40 large T antigen or a reporter gene. This would encompass any homologous FGF1B promoter from any species. However, the specification only teaches a human FGF1B promoter and mouse FGF1B promoter and does not teach any other promoter.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, human FGF1B promoter and mouse FGF1B promoter are the only species whose complete structures are disclosed. The specification does not provide any disclosure as to what would have been the structure of any other species encompassed by the claimed genus of FGF1B promoters. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, there are no other characteristics described. In regard to polynucleotides from species other than humans or mice, it

is noted that the specification does not provide any disclosure whether these sequences from other species would have had same characteristics or would have had additional characteristics or properties.

The Revised Interim Guidelines state, " when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for a mammal comprising a transgene comprising an active portion of any FGF1B promoter. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 6,7,25,26 are drawn to a transgenic mammal comprising wherein the promoter is a chimeric promoter and comprises a heterologous proximal promoter. This would encompass any heterologous proximal promoter. The specification teaches several proximal promoters; the only functional requirement is that the proximal promoter provides a basal level of transcriptional activity. However, since the basal level of transcriptional activity is undefined in the specification, the claims encompass a staggering number of promoters.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/ or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is the requirement that the heterologous proximal promoter provide a basal level of transcriptional activity. The specification contemplates several heterologous proximal promoters in addition to the minimal tk promoter (specification pg. 8); however the specification fails to identify any structural feature or functional element, common to any heterologous proximal promoters, and known at the time of filing to provide a basal level of transcriptional activity. The specification does not describe what specific nucleic acid sequence(s) or transcription factor binding sites(s) is/are required in order for a heterologous proximal promoter to provide a basal level of transcriptional activity. Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide adequate written description of the claimed genus of any transgenic mammal comprising wherein the promoter is a chimeric promoter and comprises a heterologous proximal promoter.

The Revised Interim Guidelines state, " when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for a transgenic mammal comprising wherein the promoter is a chimeric promoter and comprises a heterologous proximal promoter. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 1-11, 15-33 and 37-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome contains a transgenic construct comprising nucleotides 10 to 580 of SEQ ID NO.2, operably linked to nucleotides 5171-2533 of the SV40 large T antigen and wherein the mouse exhbits a brain tumor

whose cells lack expression of glial fibrillary acidic protein, S-100, Synaptophysin, and neuron-specific enolase, and a tumor cell line isolated from the transgenic mouse, wherein said cell line comprises said transgenic construct, does not reasonably provide enablement for any transgenic mammal whose genome comprises any FGF-1B promoter, or wherein the promoter is a chimeric promoter and comprises any heterologous proximal promoter, operably linked to any reporter gene, such as the nucleotide sequence of the SV40 large T antigen, wherein the mouse comprises a brain tumor whose cells lack immunodetectable levels of glial fibrillary acidic protein, S-100, Synaptophysin, and neuron-specific enolase, or any method for identifying any drug which is effective at inhibiting the growth of brain tumors in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claimed invention encompasses any transgenic mammal whose genome comprises any FGF-1B promoter, or wherein the promoter is a chimeric promoter and comprises any heterologous proximal promoter, operably linked to, operably linked to any reporter gene, such as the nucleotide sequence of the SV40 large T antigen, wherein the mouse comprises a brain tumor whose cells lack immunodetectable levels of glial fibrillary acidic protein, S-100, Synaptophysin, and neuron-specific enolase, a tumor cell line derived from said mammal, or any method for identifying any drug which is effective at inhibiting the growth of brain tumors in said transgenic mammal.

The specification does not provide any guidance on how to construct a transgenic mammal with the claimed phenotype of a brain tumor whose cells lack immunodetectable levels of glial fibrillary acidic protein, S-100, Synaptophysin, and neuron-specific enolase, for any

species other than a mouse. The working examples only teach that a mouse with the claimed phenotype can be constructed using a construct comprising nucleotides –540 to +31 of the human FGF-1B promoter, operably linked to nucleotides 5171-2533 of the SV40 large T antigen (Specification pg 13, example 1).

The state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic mammals comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic mammal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology, 1996) who states that '[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, lst paragraph; e.g., specific promoters, presence or absence of introns, etc.

Further, the claimed invention as filed would encompass making a transgenic mouse with any FGF-1B promoter, or wherein the promoter is a chimeric promoter and comprises any

heterologous proximal promoter, operably linked to, operably linked to any reporter gene. However, the art of making a transgenic mouse is not predictable because of several factors. For example, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in non-targeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the "transgene" (see page 256, section 4 on transgene regulation and expression). The specification supports these observations by teaching that the transgenic mouse lines built with the construct comprising nucelotides –540 to +31 of the human FGF-1B promoter, operably linked to nucleotides 5171-2533 of the SV40 large T antigen showed variation in copy number (Specification pgph 46). Further, the mouse lines showed marked variation in the distribution and size of tumors within the central nervous system (Specification pgph 49). Abnormalities in specific brain regions were also observed in specific brain regions of mice from different lines, such as 94H mice that had irregularly shaped tangles of epedymal lining in the fourth ventricle (Specification pgph 50). Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given promoter used for expressing an exogenous reporter gene in one animal would have been functional in other animals and even if the promoter may have been active, or whether the level

of the transgenic product produced would have been sufficient to produce a certain phenotype. Given the lack of teachings in the specification on how to construct any transgenic mammal with the claimed phenotype, the teachings in the art that making transgenic mammals is unpredictable and must be reduced to practice in order to reliably produce a specific phenotype, and the teachings in the art that the successful construction of a specific phenotype with a transgene in one species of mammal, is not predictive of the odds of successfully constructing a transgenic mammal of a different species with that same construct, the skilled artisan would be unable to predict how to practice the invention as claimed, except as a transgenic mouse whose genome comprises nucelotides –540 to +31 of the human FGF-1B promoter, operably linked to nucleotides 5171-2533 of the SV40 large T antigen and wherein the mouse comprises a brain tumor whose cells lack immunodetectable levels of glial fibrillary acidic protein, S-100, Synaptophysin, and neuron-specific enolase, and a tumor cell line isolated from the transgenic mouse, without extensive and undue experimentation.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a drug, which is administered by subdural injection, and is effective at inhibiting the growth of brain tumors located within the caudal pons, does not reasonably provide enablement for a method for identifying a drug, which is administered by any means, and is effective at inhibiting the growth of tumors located anywhere in the brain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification does not provide an enabling disclosure for any method of identifying any drug that is effective at inhibiting the growth of any brain tumors in any transgenic mammal with the claimed phenotype. The only mammal enabled by the specification is the transgenic mouse described above. However the specification does not provide guidance on the kinds of drugs to be administered to the mouse, the route of administration or the location of the brain tumors to be examined. No working examples describing the particulars of the claimed method are disclosed. The claimed method encompasses comparing the growth of tumors between treated and untreated mice. However, the specification teaches that even within the transgenic mice that were constructed the only highly reproducible location of tumor growth was in the caudal pons, specifically at the anterior surface of the fourth ventricle near the midline (Specification, pgph 53). Further, the mouse lines showed marked variation in the distribution and size of tumors within the central nervous system (Specification pgph 49). Therefore it would be impossible to predict whether the differences in the growth of tumors between different transgenic mouse lines was due to the drug or variations in construct expression.

The specification does not provide any guidance on the molecular size of the drugs to be administered or the route of administration of the drug. Padridge et al. teaches that the blood brain barrier formed by the capillary endothelium excludes 100% of large molecule neuorotherapeutics and more than 98% of all small-molecule drugs {Padridge et al. (2005) Neurorx. 2:3-14}. Therefore the method of administration would have enormous consequences on the kinds of drugs that could be administered according the claimed method. Given the lack of guidance in the specification on any method of identifying any drug which is effective at inhibiting the growth of any brain tumors in any transgenic mammal with the claimed phenotype,

the teachings in the specification that even in transgenic mice with the claimed phenotype substantial variation is observed in tumor growth and distribution, except at the caudal pons, the lack of guidance in the specification on any route of administration or the use of any specific molecular drug size, and the teachings in the art that the blood brain barrier formed by the capillary endothelium excludes the vast majority of drugs, the skilled practitioner would be unable to predict how to practice the claimed method without extensive and undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 15-33 and 37-40 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 20 are indefinite because the phrase "immnuodetectable levels" is vague. The specification does not make it clear what "immnuodetectable levels" mean. The term "immnuodetectable levels" in the context of the claims is dependent on the relative sensitivity of whatever immuno-assay is chosen to measure expression of the antigens. Therefore, the metes and bounds of claims 1 and 20 cannot be determined. Claims 2-11, 15-19, 37 and 39 depend on claim 1; claims 21-33, 38 and 40 depend on claim 20.

Claims 6 and 25 are indefinite because the phrase "chimeric promoter" is vague. The specification does not make it clear what "chimeric promoter" means. The organization and structure of a "chimeric promoter" is undefined by the specification. Therefore, the metes and

bounds of claims 6 and 25 cannot be determined. Claims 7 and 8 depend on claim 6; claims 26 and 27 depend on claim 25.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 9-11, 16-24, 28-33 and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alam et al. (The Journal of Biological Chemistry. Vol. 271:30263-30271, 1996) or Ray et al. (The Journal of Biological Chemistry. Vol. 272: 7546-7555, 1997) in view of Takahashi et al (Exp. Anim. 48:255-261, 1999) and Perraud et al. (Oncogene Vol. 7:993-997, 1992).

The claims are drawn to a transgenic mammal whose genome comprises any FGF-1B promoter, operably linked to any reporter gene, such as the nucleotide sequence of the SV40 large T antigen. The dependent claims recite certain nucleotides of the promoter.

At the time of the invention, Alam et al. and Ray et al. teach the characterization of the FGF1B promoter (see the entire articles). Alam et al. characterizes the expression pattern of the mouse FGF1B promoter and notes that the expression of FGF1b was in phylogenetically older brain regions, which are involved in information process and that the promoter has a role in neuronal maturation rather than in neurogenesis. Figure 5 teaches the nucleotide sequence of the promoter. The article concludes that the promoter expression is specific to brain and therefore its

expression mechanism is distinct from those in other tissues (see the last paragraph on page 30270 continued on page 30271). Ray et al. provides a more detailed analysis of the human FGF1B promoter region and discusses part of the promoter that interacts with proteins for the activation of the promoter (see the entire article). Ray et al. describes the minimal cis-acting sequence that can form DNA protein complex using FGF1B promoter driven expression constructs. Further, Ray et al. teaches the –540 to +31 of the human FGF1B promoter, which comprises –507 to +1 of the same promoter (pg. 7548, col. 1, text and Fig. 1). None of these arts teaches a mammal comprising a DNA construct comprising a transgene comprising an FGF1B promoter linked to SV40 large T antigen.

Takahashi et al. teaches a transgenic rat and rat cell lines in which expression of SV40 T antigen was under the control of a promoter and the cell lines were isolated from transgenic rats that were produced by integrating the construct comprising SV40 promoter driving the expression of SV40 large T antigen (see the abstract and the rest of the articles). The art also teaches that to make a cell line, it is advantageous to express immortalizing oncogenes such as large T antigen in the cells (see the introduction on page 255 continued on page 256 and the discussion). Perraud et al. teaches the construction of vectors comprising a promoter driving the expression of SV40 long T antigen to study the potential oncogenesis associated with tissue-specific activity of the promoter for CFTR gene.

At the time of the invention, it would have been obvious to an artisan of ordinary skill to modify the construct of Takashi et al. by replacing the promoter with the FGF1B promoter taught by Ray et al. or Alam et al., in order to make a transgenic rodent, with a reasonable expectation of success. An artisan would have been motivated to make such transgenic mice or rats because

it would have allowed the study of brain specific expression of the FGF1B promoter and cell lines which could provide in vivo model for studying the promoter function.

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dr. Louis D. Lieto
Patent Examiner
Art Unit 1632

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER

Continuation of Attachment(s) 6). Other: Notice to comply with sequence requirement.

Application No.: 10/829491

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: There is no record of submission an updated CRF including SEQ ID NO: 3.

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE